4 November 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News– Pandemic Influenza Supplement #34

1. PERFORMANCE OF BINAX NOW FLU A AND B AND DIRECT FLUORESCENT ASSAY IN COMPARISON WITH A COMPOSITE OF VIRAL CULTURE OR REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION FOR DETECTION OF INFLUENZA INFECTION DURING THE 2006 TO 2007 SEASON: *"During the 2006 to 2007 influenza season, DFA and Binax NOW demonstrated high specificity but failed to identify a substantial proportion of influenza infections."*

2. RAPID TYPING, SUBTYPING AND RNA QUANTIFICATION OF INFLUENZA VIRUS TYPE A STRAINS IN RESPIRATORY SECRETIONS: *"Typing and subtyping of influenza virus type A strains may benefit from both MAbs and RT-PCR, while viral RNA quantification may provide an indication of symptom onset."*

3. DIRECTIONALITY IN THE EVOLUTION OF INFLUENZA A HAEMAGGLUTININ: *"Our results suggest that the evolution of the influenza A HA, including evolution by positive selection, is strongly affected by the long-term site-specific preferences for individual amino acids."*

4. CLEARANCE OF INFLUENZA VIRUS FROM THE LUNG DEPENDS ON MIGRATORY LANGERIN(+)CD11B(-) BUT NOT PLASMACYTOID DENDRITIC CELLS: *"This suggests that multiple DCs [dendritic cells] are endowed with different tasks in mediating protection against influenza virus."*

5. LOCAL NOT SYSTEMIC MODULATION OF DENDRITIC CELL S1P RECEPTORS IN LUNG BLUNTS VIRUS-SPECIFIC IMMUNE RESPONSES TO INFLUENZA: *"Thus, our results suggest that locally delivered sphingosine analogs induce immunosuppression by modulating S1P receptors other than S1P(1) or S1P(2) on dendritic cells in the lungs after influenza virus infection."*

6. CLEAVAGE MECHANISM OF THE H5N1 HEMAGGLUTININ BY TRYPSIN AND FURIN: *"These findings hint that we should focus at the subsites P-1, P-4, and P-6 for*

developing drugs against H5N1 viruses."

7. INDONESIA SAYS PANDEMIC THREAT REMAINS AS DEATHS EASE: *"The government has started work on its own H5N1 vaccine and allocated 700 billion rupiah ($64 million) in next year's budget to prepare for a pandemic, including building facilities to produce inoculations, Health Minister Siti Fadilah Supari said."*

CB Daily Report

Chem-Bio News

PERFORMANCE OF BINAX NOW FLU A AND B AND DIRECT FLUORESCENT ASSAY IN COMPARISON WITH A COMPOSITE OF VIRAL CULTURE OR REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION FOR DETECTION OF INFLUENZA INFECTION DURING THE 2006 TO 2007 SEASON
Virus Weekly
November 4, 2008

"The Binax NOW Flu A and Flu B (Binax NOW), direct fluorescent assay (DFA), and viral culture were evaluated and compared with a composite of viral culture or reverse transcription polymerase chain reaction (RT-PCR). Participants with medically attended acute respiratory illness were identified through active surveillance during the 2006 to 2007 season, and consenting individuals (n=932) were tested for influenza by culture and RT-PCR."

"Physicians ordered a rapid antigen test (Binax NOW [n=73] or DFA [n=70]) according to their clinical judgment. The Binax NOW detected 11 of 18 influenza infections (sensitivity, 61%; 95% confidence interval [CI], 36-83%), whereas DFA detected 17 of 21 influenza infections (sensitivity 81%, 95% CI, 58-95%). Compared with culture/RT-PCR, specificity of both Binax NOW and DFA was 100%."

"During the 2006 to 2007 influenza season, DFA and Binax NOW demonstrated high specificity but failed to identify a substantial proportion of influenza infections."

The full article can be found at: (M. Rahman, et. al., "Performance of Binax NOW Flu A and B and direct fluorescent assay in comparison with a composite of viral culture or reverse transcription polymerase chain reaction for detection of influenza infection during the 2006 to 2007 season". Diagnostic Microbiology and Infectious Disease, 2008;62(2):162-6). Link not available.

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RAPID TYPING, SUBTYPING AND RNA QUANTIFICATION OF INFLUENZA VIRUS TYPE A STRAINS IN RESPIRATORY SECRETIONS
Hospital Business Week

November 2, 2008

“"During the winter-spring season 2006-2007, 38 influenza virus strains were identified in patients admitted to hospital with an acute respiratory tract infection. Infections were diagnosed in parallel by direct fluorescent antibody (DFA) staining using type-specific monoclonal antibodies and real-time reverse transcription (RT)-PCR targeting the gene M (nt 25-124)."

"In addition, virus strains were isolated in MDCK cells. Overall, 37 influenza virus strains were type A, and one type B. Of these, 35 (80.4%) were detected and typed by real-time RT-PCR, 34 (80.1%) by DFA, and 27 (71.0%) by virus isolation. Subtyping of 37 influenza virus A strains by RT-PCR and DFA gave the following results: 4/6 H1 strains were correctly subtyped by both methods, while of the 29 H3 strains subtyped by RT-PCR 7 were missed by DFA. Thus, the overall concordance of the two subtyping methods was 28/37 (75.7%). Viral RNA quantification by real-time PCR showed that when respiratory secretion collection was done within 5 days after the onset of symptoms, viral load was greater than 1 x 106 RNA copies/ml."

"Typing and subtyping of influenza virus type A strains may benefit from both MAbs and RT-PCR, while viral RNA quantification may provide an indication of symptom onset."

The full article can be found at: (E. Percivalle, et. al., “Rapid typing, subtyping and RNA quantification of influenza virus type A strains in respiratory secretions”. The New Microbiologica, 2008;31(3):319-27). Link not available.

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DIRECTIONALITY IN THE EVOLUTION OF INFLUENZA A HAEMAGGLUTININ
Drug Week
November 7, 2008

“Many characteristics of HA's sequence evolution are captured by standard Markov chain substitution models."

"Such models assign equal fitness to all accessible amino acids at a site. We show, however, that such models strongly underestimate the number of homoplastic amino acid substitutions during the course of HA's evolution, i.e. substitutions that repeatedly give rise to the same amino acid at a site. We develop statistics to detect individual homoplastic events and find that they preferentially occur at positively selected epitopic sites."

"Our results suggest that the evolution of the influenza A HA, including evolution by positive selection, is strongly affected by the long-term site-specific preferences for individual amino acids."

The full article can be found at: (S. Kryazhimskiy, et. al., “Directionality in the evolution of influenza A haemagglutinin”. Proceedings, 2008;275(1650):2455-64). Link not available.

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CLEARANCE OF INFLUENZA VIRUS FROM THE LUNG DEPENDS ON MIGRATORY LANGERIN(+)CD11B(-) BUT NOT PLASMACYTOID DENDRITIC CELLS
Virus Weekly
November 4, 2008

"Although dendritic cells (DCs) play an important role in mediating protection against influenza virus, the precise role of lung DC subsets, such as CD11b(-) and CD11b(+) conventional DCs or plasmacytoid DCs (pDCs), in different lung compartments is currently unknown. Early after intranasal infection, tracheal CD11b(-)CD11c(hi) DCs migrated to the mediastinal lymph nodes (MLNs), acquiring co-stimulatory molecules in the process."

"This emigration from the lung was followed by an accumulation of CD11b(+)CD11c(hi) DCs in the trachea and lung interstitium. In the MLNs, the CD11b(+)DCs contained abundant viral nucleoprotein (NP), but these cells failed to present antigen to CD4 or CD8 T cells, whereas resident CD11b(-)CD8 alpha(+) DCs presented to CD8 cells, and migratory CD11b (-)CD8 alpha(-) DCs presented to CD4 and CD8 T cells. When lung CD11c(hi) DCs and macrophages or langerin(+)CD11b(-)CD11c(hi) DCs were depleted using either CD11c-diphtheria toxin receptor (DTR) or langerin-DTR mice, the development of virus-specific CD8 (+) T cells was severely delayed, which correlated with increased clinical severity and a delayed viral clearance. 120G8(+) CD11c(int) pDCs also accumulated in the lung and LNs carrying viral NP, but in their absence, there was no effect on viral clearance or clinical severity. Rather, in pDC-depleted mice, there was a reduction in antiviral antibody production after lung clearance of the virus."

"This suggests that multiple DCs are endowed with different tasks in mediating protection against influenza virus."

The full article can be found at: (C.H. Geurtsvankessel, et. al., “Clearance of influenza virus from the lung depends on migratory langerin(+)CD11b(-) but not plasmacytoid dendritic cells”. Journal of Experimental Medicine, 2008;205(7):1621-1634). Link not available.

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LOCAL NOT SYSTEMIC MODULATION OF DENDRITIC CELL S1P RECEPTORS IN LUNG BLUNTS VIRUS-SPECIFIC IMMUNE RESPONSES TO INFLUENZA
Drug Week
November 7, 2008

“In this report, we show that intratracheal delivery of the chiral sphingosine analog (R)-2-amino-4-(4-heptyloxyphenyl)-2methylbutanol (AAL-R) or its phosphate ester inhibits the T-cell response to influenza virus infection."

"In contrast, neither intraperitoneal delivery of AAL-R nor intratracheal instillation of the

nonphosphorylatable stereoisomer AAL-S suppressed virus-specific T-cell response, indicating that in vivo phosphorylation of AAL-R and sphingosine 1-phosphate (S1P) receptor modulation in lungs is essential for immunomodulation. Intratracheal delivery of water-soluble S1P 1 receptor agonist at doses sufficient to induce systemic lymphopenia did not inhibit virus-specific cell response, indicating that S1P(1) is not involved in the immunosuppressive activities of AAL-R and that immunosuppression acts independently of naive lymphocyte recirculation. Accumulation of dendritic cells (DCs) in draining lymph nodes was inhibited by intratracheal but not intraperitoneal delivery of AAL-R. Direct modulation of DCs is demonstrated by the impaired ability of virus-infected bone marrow-derived DCs treated in vitro with AAL-R to trigger in vivo T-cell response after adoptive transfer to the airways."

"Thus, our results suggest that locally delivered sphingosine analogs induce immunosuppression by modulating S1P receptors other than S1P(1) or S1P(2) on dendritic cells in the lungs after influenza virus infection."

The full article can be found at: (D. Marsolais, et. al., “Local not systemic modulation of dendritic cell S1P receptors in lung blunts virus-specific immune responses to influenza”. Molecular Pharmacology, 2008;74(3):896-903). Link not available.

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CLEAVAGE MECHANISM OF THE H5N1 HEMAGGLUTININ BY TRYPSIN AND FURIN
Biotech Week
November 5, 2008

"The cleavage property of hemagglutinin (HA) by different proteases was the prime determinant for influenza A virus pathogenicity. In order to understand the cleavage mechanism, molecular modeling tools were utilized to study the coupled model systems of the proteases, i.e., trypsin and furin and peptides of the cleavage sites specific to H5N1 and H1 HAs, which constitute models of HA precursor in complex with cleavage proteases."

"The peptide segments 'RERRRKKR down arrow G' and 'SIOSR down arrow G' from the high pathogenic H5N1 H5 and the low pathogenic H1N1 H1 cleavage sites were docking to the trypsin and furin active pockets, respectively. It was observed through the docking studies that trypsin was able to recognize and cleave both the high pathogenic and low pathogenic hemagglutinin, while furin could only cleave the high pathogenic hemagglutinin. An analysis of binding energies indicated that furin got most of its selectivity due to the interactions with P-1, P-4, and P-6, while having less interaction with P-2 and little interactions with P-3, P-5, P-7, and P-8. Some mutations of H5N1 H5 cleavage sequence fitted less well into furin and would reduce high pathogenicity of the virus."

"These findings hint that we should focus at the subsites P-1, P-4, and P-6 for developing drugs against H5N1 viruses."

The full article can be found at: (X.L. Guo, et. al., “Cleavage mechanism of the H5N1 hemagglutinin by trypsin and furin. Amino Acids, 2008;35(2):375-382)”. Link not available.

ANALYST NOTE: Readers may wish to refer to: "The H5N1 Influenza Variant Fujian-Like Hemagglutinin Selected Following Vaccination Exhibits A Compromised Furin Cleavage", which was highlighted in the previous edition of the CB Daily – Pandemic Influenza Supplement No. 33, dated 28 Oct. 08 for a related article.

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INDONESIA SAYS PANDEMIC THREAT REMAINS AS DEATHS EASE
By Leony Aurora and Naila Firdausi
Bloomberg News
November 3, 2008

"Indonesia, the nation with the most bird flu deaths, said the threat of a deadly flu pandemic hasn't passed even though no new human cases of the H5N1 virus have been detected in the archipelago since July.

The government has started work on its own H5N1 vaccine and allocated 700 billion rupiah ($64 million) in next year's budget to prepare for a pandemic, including building facilities to produce inoculations, Health Minister Siti Fadilah Supari said. The nation may also resume sharing H5N1 samples with the world next year if it can complete an agreement at a World Health Organization meeting next month."

"Negotiations to resume virus-sample sharing ``have come a long way,'' Supari said. ``The only obstacle left is the choice of tracking system,'' she said. Indonesia expects to reach an agreement on changes to the WHO's Global Influenza Surveillance Network at a meeting in Geneva in December and may resume virus- sharing next year, she said.

It's at least the second time Supari has promised to resume sharing virus samples. In March 2007 she said Indonesia would recommence virus-sharing ``immediately.'' In August last year the WHO said it was yet to receive any samples."

The full article can be found at: http://www.bloomberg.com/apps/news?pid=20601080&sid=acboyNqM6t_U&refer=asia

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Steve Tesko: Steve.Tesko@anser.org

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